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23690	7590	11/28/2006	EXAMINER	
Roche Diagnostics OPERATIONS Inc. 9115 Hague Road PO Box 50457 Indianapolis, IN 46250-0457			FOSTER, CHRISTINE E	
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			1641	

DATE MAILED: 11/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

10/774,325

Applicant(s)

FINKE ET AL.

Examiner

Christine Foster

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 09 October 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-3, 5 and 9-19 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-3, 5, and 9-19 is/are rejected.
- 7) ☒ Claim(s) 12, 16, 17 and 19 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

## Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
- 1) ☒ Certified copies of the priority documents have been received.
  - 2) ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - 3) ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

## Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

## **DETAILED ACTION**

### ***Response to Amendment***

1. Applicant's amendment filed on 7/17/06 is acknowledged and has been entered. The corrected reply of 10/9/06 is further acknowledged. The examiner thanks Applicant for addressing the patentability of the newly added claims over the references of record in the corrected reply.
2. Claim 1 has been amended. Claims 9-19 were added. Claims 1-3, 5, and 9-19 are currently pending and under examination.

### ***Objections/Rejections Withdrawn***

3. The objections to claim 1 set forth in the previous Office action are withdrawn in response to Applicant's amendments.
4. The rejection of claim 1 under 112, 2<sup>nd</sup> paragraph set forth in the previous Office action has been obviated by the amendments.
5. The rejections of claims 1-2 under 35 USC 103(a) as being unpatentable over Lou et al. are withdrawn in response to the amendments to claim 1; the reference has now been applied under 35 USC 102(b).

### ***Claim Objections***

6. Claims 12, 16-17 and 19 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is

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required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

7. Claims 16-17 and 19 are objected to for the following reasons. Claim 15 recites a method “**consisting of the steps of**” (a) and (b) that follow. The use of the closed transitional phrase “**consisting of**” limits the scope of the claim to the specified steps that follow and excludes any element, step, or ingredient not specified in the claim. See MPEP 2111.03. However, claim 16 (which depends from claim 15) recites a method “further comprising the step of incubating...”. The dependent claim recites an additional step and is therefore broader in scope than the parent claim, which is improper. Similarly, claim 19 recites that “the pH of said suspension is adjusted to a pH value between 10.0 and 12.5”, which appears to represent an active method step. Claim 17 recites that “said coating step is conducted with a buffer...”, yet there is no mention of a buffer ingredient in claim 15.

For the purposes of examination claim 15 has been construed as a method “comprising” the recited steps.

8. Claim 12 is objected to because of the following informalities: the claim refers to the pH of “said **suspension**”, while independent claim 1 refers to the pH of “said **combination**”. For the purposes of examination the pH recited in claim 12 was assumed to refer to the pH of the combination of microparticles and protein and not to the pH of the uncoated microparticle suspension.

9. Claim 15 recites in part (a) that “...the pH of said suspension between...”. It appears that the phrase should read “...the pH of said suspension is between...”

***Claim Rejections - 35 USC § 112***

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-3, 5, 9, 13-14, and 17-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Applicant's amendment, filed 2/21/06 asserts that no new matter has been added and indicates that support for the amendments to claim 1 may be found in the specification in Examples 1 and 2 at paragraphs 45-46.

12. Claim 1 as originally filed recited combining a suspension of uncoated microparticles with a protein, where the suspension comprised a buffer having a pH of 10 to 12.5. The specification discloses that the coating reaction is preferably carried out at a pH between 10 and 12.5 at [0015].

Claim 1 now recites that the pH of the combination (of microparticles and protein) is between pH 10.5 to 12.5.

The specification discloses a general teaching that the coating reaction is carried out at pH 10-12.5 [0015]. The specification also discloses the specific range of pH 10.5-12.5 at [0030]. However, when this particular pH range of 10.5-12.5 is mentioned, it is in the context of *long coating intervals* of 1-10 or 4-7 days:

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It is particularly preferable to carry out the coating for 4 - 7 days. When using these relatively long time intervals, pH ranges of 10.5 to 12.5 and in particular of 11.0 to 12.0 are particularly preferred.

Claim 1 now recites the pH range of 10.5-12.5 but makes no mention of a time interval of 1-10 or 4-7 days. This represents new matter because the claim is now drawn to a broad genus of methods carried out at pH 10.5-12.5 (which could be carried out for any period of time) which is broader in scope than the disclosure, which teaches the pH range of 10.5-12.5 only in the context of a 1-10 or 4-7 day coating. In other words, Applicant's incorporation of the pH limitation of 10.5-12.5 without the accompanying limitation of 1-10 or 4-7 days disclosed in the specification has effectively created a new subgenus (pH 10.5-12.5) that is not supported by either the generic teaching (pH 10-12.5) or by the specific teaching (pH 10.5-12.5 with 1-10 or 4-7 day coating). Disclosure of a genus and species of subgenus within that genus is not sufficient description of subgenus to satisfy description requirement of 35 U.S.C. 112, unless there are specific facts which lead to determination that subgenus is implicitly described. *Ex parte Westphal*, 26 USPQ2d (BPAI 1993). *In re Smith* 173 USPQ 679 (CCPA 1972).

13. With respect to claims 14 and 19, which recite the step of **adjusting the pH of the combination** from 10.5 to 12.5, Applicant has indicated that the specification provides support for this limitation in Examples 1-2. In Example 1, [0045], the specification discloses that following combination of DYNAL M-270 or M-280 magnetic beads with polymerized streptavidin, the pH was then adjusted to the desired value between pH 10.0 and pH 12.5 with NaOH. Similarly, at [0046], the specification discloses that following the combination of DYNAL M-270 or M-280 magnetic beads with polymerized streptavidin, the pH was then adjusted to the desired value between pH 10.0 and pH 12.5 with NaOH. Thus, the specification

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discloses the step of adjusting the pH only in the context of adjusting the pH of a combination of DYNAL M-270 or M-280 magnetic beads with polymerized streptavidin to between pH 10.0 and pH 12.5. Note that in the specific examples in which the pH is adjusted, it is adjusted to between 10 and 12.5 and not to between 10.5 and 12.5 as now recited in claim 14.

The incorporation of the step of adjusting the pH into the claims has effectively created a new subgenus (adjusting the pH of the combination of microparticles with a protein, and adjusting the pH by any means) that is not supported by the specific teaching of particular types of microparticles, a particular protein, and a particular pH range (adjusting the pH of the combination of DYNAL M-270 or M-280 magnetic beads with polymerized streptavidin to between pH 10.0 and pH 12.5 with NaOH). There is also no support in the specification for the step of adjusting the pH to between 10.5 and 12.5 since the specification only discloses adjusting the pH to between 10 and 12.5.

14. Claim 2 as originally filed recited that the protein is in a **polymerized form**. The amendment filed 10/6/05 amended the claim to recite that the protein has been polymerized by chemical treatment. The specification at [0027] states that:

Polymerization of streptavidin can be achieved in a known matter by chemical treatment. Polymerized avidin or streptavidin and particularly preferably polymerized streptavidin is preferably used in a coating method according to the invention. Polymerized antibodies are also particularly suitable.

The above passage provides support for polymerized streptavidin (and possibly also avidin) that has been polymerized by chemical treatment. There is no generic teaching in the specification of polymerization of *proteins in general* by chemical treatment. Although the specification refers to “polymerized proteins” at [0026], there is no mention of chemical treatment of “polymerized proteins” in the specification. Therefore, the recitation in claim 2 of

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“protein” that has been polymerized by chemical treatment represents the introduction of a subgenus of “proteins polymerized by chemical treatment” that is not supported by the disclosure of “streptavidin polymerized by chemical treatment”.

15. New claim 17 recites that the coating step is conducted with a buffer “having a salt content of **about 0.3 to about 1.5 M**”. The specification discloses at [0031] that:

The coating is preferably carried out with a buffer which has a salt content of 0.1 to 2 M, particularly preferably 0.3 to 1.5 M and especially preferably of 0.8 to 1.2 M.

The specification does not fully support the claimed subject matter because the range “**about 0.3 to about 1.5 M**” is broader in scope than the disclosure of “**0.3 to 1.5 M**”.

16. New claim 18 recites that “the microparticles have a size of about 2.8  $\mu\text{m}$  and consist essentially of about 88% polystyrene and 12% magnetite”. Applicant’s response stated that no new matter was added (p. 4) but did not specifically indicate where support could be found for the new claim. The specification discloses at [0022]:

DYNABEADS from the DYNAL Company having a size of ca 2.8  $\mu\text{m}$  and consisting of 88% polystyrene and 12% magnetite such as the hydrophobic beads M-280 or the epoxy beads M-270 are, for example, suitable.

The new claim represents new matter because (1) the transitional phrase “**consisting essentially of**” defines a different scope than “**consisting of**” as disclosed in the specification (see MPEP 2111.03). Further, the claimed “**about 88%**” is different than the disclosed “88%”. There is no description of uncoated polystyrene microparticles “consisting essentially of about 88% polystyrene and 12% magnetite”.

In addition, the examples of M-270 and M-280 as in the above passage would seem to be directed to **coated** rather than **uncoated** microparticles. See the specification at paragraph 3, and also Hornes et al. (US 5,512,439), columns 3-4, and especially at column 4, lines 25-31, which

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describes the functionalized coatings of hydroxyl groups on M-280 DYNABEADS. Thus there appears to be no disclosure of **uncoated** microparticles having the recited composition.

Additionally, the passage above discloses the claimed size and composition only in describing the properties of “**DYNABEADS**”. This description of DYNABEADS having the recited size and composition does not fully support the claim, which now encompasses **all microparticles** with a size of about 2.8  $\mu\text{m}$  that consist essentially of about 88% polystyrene and 12% magnetite.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

17. Claims 1-3, 5, and 9-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

18. The term “**strongly alkaline**” in claims 1 and 15 is a relative term that renders the claims indefinite. The term “strongly alkaline” is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Although the claims also recite specific pH ranges, it is not clear that the specified ranges are intended to define the “strongly alkaline” conditions recited. For example, claim 1 recites “combining...microparticles with a protein to form a combination” in part (a) and later recites in part (b) the step of “coating the protein onto the microparticles by adsorption under strongly alkaline conditions, wherein the pH of said combination is between 10.5 and 12.5”. The claim

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requires only that the combination have a pH between 10.5 and 12.5, but does not explicitly state that the coating step also takes place at this pH range. As a result, the claim does not rule out a scenario where the initial pH of the combination is 10.5-12.5, and then the coating is carried out at a different, "strongly alkaline" pH.

Similarly, in claim 15 the claim recites "forming a suspension...in the presence of strongly alkaline conditions", but it is not entirely clear that the later-recited pH range of "between 10.0 and 12.5" is intended to define the scope of "strongly alkaline". Because the claims do not clearly tie "strongly alkaline" together with the recited pH ranges, and because the specification does not provide a limiting definition for this term, one skilled in the art would not know what ranges were encompassed by "strongly alkaline".

19. Claims 1 and 15 are also indefinite because they recite the broad recitation "strongly alkaline" together in the same claim with "pH...between 10.5 and 12.5" or "pH...between 10.0 and 12.5", which are narrower statements of the range/limitation. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note

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also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949).

If Applicant wishes to use the term “strongly alkaline” in the claims as a way to characterize or describe the recited pH ranges, it is suggested that the term may be employed in the preamble.

### ***Claim Rejections - 35 USC § 102***

20. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

21. Claims 15 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Vaynberg et al. in light of Bocquier et al. and Bohidar, all of record.

The examiner notes that the preamble of claim 15 recites a method “**consisting of**” the recited steps, which would exclude any element, step, or ingredient not specified in the claim (see the objections to claims 16-17 and 19 above). However, since claims 16-17 and 19 do in fact recite additional elements/steps, it appears that Applicant does not intend claim 15 to be restricted only to the recited steps and elements. Therefore, for the purposes of examination, claim 15 has been interpreted as being drawn to a method “**comprising**” the recited steps.

Vaynberg et al. teach a method for producing protein-coated polystyrene microparticles that includes the steps of combining a suspension (colloid) of uncoated microparticles with a polymerized protein that is a member of a bioaffinity binding pair (gelatin) in pH 10 buffer to

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coat the gelatin onto the microparticles by adsorption. Vaynberg et al. further teach separating the non-adsorbed protein from the protein-coated microparticles (by centrifugation) (see the entire document, in particular at p. 467-468, the section "Adsorption Isotherms" and Table 1; p. 468-469, the section "Adsorption Thermodynamics"; p. 470-471, the section "Adsorption Isotherms"; and Figures 2 and 8).

The Bocquier et al. and Bohidar et al. references are relied upon as evidentiary references teaching inherent properties of the protein of Vaynberg et al. (gelatin), specifically that the protein is a member of a "bioaffinity binding pair" and has a size from 10 nm to 300 nm. First, Bocquier et al. evidence that the protein gelatin is a partner of a bioaffinity binding pair as it binds fibronectin (see Bocquier et al., p. 1451, column 2, lines 1-10). Second, gelatin has a size within the recited range of 10 nm to 300 nm as evidenced by Bohidar, in particular at p. 4, Table 2. The reference evidences that gelatin has a size within the recited parameters since the radius values reported therein are in the recited range. In particular, the hydrodynamic radius  $R_{e,D}$  is 190-280 Å, which is equivalent to 19.0-28.0 nm (Table 2).

With respect to claim 17, Vaynberg et al. teach that the pH of the gelatin stock solution was adjusted using 1M acetic acid or 0.1M NaOH prior to mixing with the polystyrene microparticles (p. 468, left column, the first paragraph). This reads on the claim because although in the reference the gelatin-polystyrene microparticle mixtures were prepared in 10 mM NaAc buffer, the claim only requires that the coating step is conducted "with" a buffer having the recited salt content and does not exclude the teaching of Vaynberg et al. in which such a buffer was used to adjust the pH of the protein solution prior to mixing.

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22. Claims 1-2, 13, 15 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Lou et al. (US 4,329,151) in light of Rossjohn et al. ("Structure of a Cholesterol-Binding, Thiol-Activated Cytolysin and a Model of Its Membrane Form" *Cell* 89:685-692 (1997) and Weis et al. ("Streptolysin O: the C-terminal, tryptophan-rich domain carries functional sites for both membrane binding and self-interaction but not for stable oligomerization" *Biochimica et Biophysica Acta* 1510 (2001) 292-299).

Lou et al. teach a method for producing protein-coated polystyrene latex microparticles, comprising combining a suspension of polystyrene latex particles with a protein (streptolysin-O) (see the abstract; column 2, lines 55-57; column 3, lines 40-62; column 6, lines 9-15 and 29-46). Lou et al. further teach incubating the combination of microparticles and protein in a buffer solution with a pH range of from about 8.5 to about 11.9 for a period of time whereby the protein is coated onto the microparticles by adsorption (column 4, lines 34-43 and 49-63). Lou et al. further teach separating the non-adsorbed protein from the protein-coated microparticles by a wash step followed by centrifugation of the particles (column 5, lines 48-60). Streptolysin-O is a partner of a bioaffinity binding pair in that it is capable of binding to antibodies (column 1, lines 24-29).

Regarding the limitation that "the pH of [the protein-microparticle combination] is between 10.5 and 12.5" as in claim 1 and that "the pH of said suspension [is] between 10.0 and 12.5" as in claim 15, Lou et al. teach that the coating reaction is maintained at the desired pH by diluting the protein into a buffered solution of the desired pH (column 4, lines 49-53; column 6, lines 29-31 and 40-42) before it is mixed with the microparticles. It is noted that the buffer is employed at 0.5 M strength (see column 3, lines 63-68; column 4, lines 59-62). Further, the

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protein diluted into the buffer is mixed with a much smaller volume of the microparticle suspension, which is provided unbuffered in water (Example 1; column 5, lines 48-63). Thus, it would be immediately apparent to one skilled in the art that the pH of the microparticle-protein suspension would also be maintained at the buffer pH, i.e. 8.5 to 11.9.

Lou et al. fail to specifically state that the streptolysin-O has a size from 10 nm to 300 nm. However, the factual evidence reasonably supports the determination that streptolysin-O is inherently a protein of this size for the following reasons.

A search of the literature in order to determine the size of streptolysin-O protein found the Rossjohn et al. and Weis et al. references, which are relied upon to support the Examiner's position that the streptolysin-O protein used by Lou et al. does in fact have a size from 10 nm to 300 nm. Weis et al. teach that streptolysin-O belongs to a class of structurally related thiol-activated toxins (the abstract). While it appears that the exact size of streptolysin-O has not been determined by X-ray crystallography, Weis et al. teach that the X-ray structure another member of this class, perfringolysin-O, has been determined (Weis et al., p. 292; p. 295, Figure 1A and accompanying legend). In particular, Weis et al. teach that the structure of the streptolysin-O monomer has been modeled based on the crystal structure of the homologous perfringolysin-O. Thus, Weis et al. teach that the structure of streptolysin-O may be approximated based on the structure of perfringolysin-O since these proteins are highly homologous.

Rossjohn et al. is the publication referred to by Weis et al. as describing the structure of perfringolysin-O (Weis et al., p. 292). Rossjohn et al. also teach that perfringolysin-O is a member of a class of toxins (including streptolysin-O) that are highly homologous, "suggesting they will all have very similar 3D structures" (p. 685, "Introduction"). Rossjohn et al. teach that

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perfringolysin-O is an unusually elongated rod-shaped molecule with dimensions of 115 x 30 x 55 Angstroms (p. 685, right column, "Overall Structural Features"). Since 1 Angstrom = 0.1 nm, perfringolysin-O has dimensions of 11.5 x 3 x 5.5 nm, which are within the claimed size range of 10 nm to 300 nm. In light of the teaching in Weis et al. that the structure of streptolysin-O may be inferred by reference to the structure of perfringolysin-O, and also the teaching in Rossjohn et al. that the toxin family members are expected to have very similar 3D structures, one skilled in the art would reasonably conclude that streptolysin-O has very similar dimensions to that of perfringolysin-O and therefore meets the claimed size range.

With respect to claim 13, Lou et al. teach 0.5M Boric Acid-KCl-NaOH buffer (column 3, lines 63-68).

### ***Claim Rejections - 35 USC § 103***

23. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

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This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

24. Claims 1, 9 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vaynberg et al. in light of Bocquier et al. and Bohidar.

Vaynberg et al. teach a method for producing protein-coated polystyrene microparticles that includes the steps of combining a suspension (colloid) of uncoated microparticles with a polymerized protein that is a member of a bioaffinity binding pair (gelatin), the combination comprising a buffer of pH 10, incubating the combination for a period of time whereby the protein is coated onto the microparticles by adsorption, and separating the non-adsorbed protein from the protein-coated microparticles (by centrifugation) (see p. 467, column 2, lines 30-32 and the section "Materials," lines 9-16; p. 468, column 1, lines 1-4, 15-31, and Table 1; p. 469, column 1, lines 1-7, and column 2, lines 25-29; and p. 470, Figure 8).

Vaynberg et al. do not specifically recite a reaction pH of pH 10.5 to 12.5. Rather, Vaynberg et al. teach adsorption of gelatin onto the polystyrene particles at various pH values up to pH 10 (Figures 1-7). However, MPEP 2144.05 states that:

...a prima facie case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties. *Titanium Metals Corp. of America v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985)

and further that:

Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)

In the instant case, it would have been obvious to one of ordinary skill in the art to employ slightly higher pH values (for example, pH 10.5) through routine optimization/experimentation of the conditions of Vaynberg et al. with a reasonable expectation of success, because of the normal desire of scientists or artisans to improve upon what is already generally known. In addition, one would be motivated to employ higher pH values because Vaynberg teaches that because hydrophobic effects dominate in adsorption of gelatin, increasing pH enables a denser layer of gelatin to form on the polystyrene (p. 471, left column, first full paragraph).

One would have reasonable expectation of success in employing higher pH values in the method of Vaynberg et al. because Vaynberg et al. repeatedly teach that pH differences were not critical and produced *little variation in the adsorption efficiency* of gelatin onto the polystyrene (p. 469, right column, line 25 to p. 470, left column and Figures 2-3). In particular, Vaynberg et al. teach that "pH hardly affects the adsorption of gelatin to [polystyrene]" (p. 470, left column, lines 12-13) and further note "the ability of gelatin to adsorb to [polystyrene] even at high electrolyte and high pH conditions" (p. 471, right column, second paragraph).

The Bocquier et al. and Bohidar et al. references are relied upon as evidentiary references teaching that the protein of Vaynberg et al., fulfills the limitations of being a partner of a

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bioaffinity binding pair and having a size from 10 nm to 300 nm as recited in claim 1. The protein gelatin is a partner of a bioaffinity binding pair as it binds fibronectin (see Bocquier et al., p. 1451, column 2, lines 1-10). Gelatin has a size within the recited range of 10 nm to 300 nm as evidenced by Bohidar, in particular at p. 4, Table 2. Bohidar evidences that gelatin has a size within the recited parameters since the radius values reported therein are in the recited range. In particular, the hydrodynamic radius  $R_{e,D}$  is 190-280 Å, which is equivalent to 19.0-28.0 nm (Table 2). This reads on claim 9 since a radius of 19-28 nm would mean a length that is twice this value (38-56 nm).

The limitation of claim 13 is met as discussed above under 35 USC 102 with respect to claim 17. In addition, examiner would also note that Vaynberg et al. investigated electrolyte effects (i.e. buffer concentration) and report that adsorption to polystyrene increases with increasing salt up to 100 mM and then plateaus (Figure 9; p. 470, right column). As such, it would have been obvious to vary the buffer concentration (e.g. to employ 100 mM salt in place of 10 mM salt) as part of routine optimization because of the normal desire of artisans to improve upon what is already known, and especially in light of the fact that the reference teaches that adsorption to polystyrene is increased with increasing buffer concentration. There is no evidence of record to the effect that such differences in buffer concentration are critical.

25. Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Vaynberg et al. in light of Bocquier et al. and Bohidar as applied to claim 1 above, and in view of Tischer et al. (US Patent No. 5,061,640).

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Vaynberg et al. is as discussed above, which fails to teach a protein that has been polymerized by chemical treatment.

Tischer et al. teach a process for the preparation of a protein for adsorption to an insoluble carrier material such as polystyrene (see column 2, lines 25-34 and column 4, lines 19-38). In particular, Tischer et al. teach polymerizing of proteins to be adsorbed using a cross-linking compound (column 3, lines 32-39 and 63-68; column 4, lines 1-7; column 8, Example 2, lines 38-42; and column 9, part (d), lines 9-10). Tischer et al. further teach that this polymerizing of proteins has the effect of increasing their molecular weights (column 3, lines 32-43), which results in improved adsorption of the proteins to the insoluble carrier material (see column 2, lines 35-37).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to include the step of polymerizing gelatin by treatment with a cross-linking compound, as taught by Tischer et al., in the method for producing protein-coated microparticles of Vaynberg et al. in order to increase the molecular weight of gelatin and thereby improve the adsorption of gelatin to polystyrene. One would have reasonable expectation of success because Tischer et al. teach the step of increasing the molecular weight in preparation for coating proteins onto polystyrene by adsorption, which is the object of the method of Vaynberg et al.

26. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Vaynberg et al. in light of Bocquier et al. and Bohidar as applied to claim 1 above, and in view of Desai et al. (US 6,638,728 B1).

Vaynberg et al. fail to teach a method where the protein coated is streptavidin that has been polymerized by chemical treatment.

Desai et al. teach methods for producing surfaces such as polystyrene spheres that are coated with streptavidin that has been polymerized by treatment with a chemical cross-linking reagent, (see in particular column 1, lines 25-30 and 60-67; column 2, lines 17-34; column 2, line 65 to column 3, line 24). Desai et al. teach that such surfaces are useful in capturing target molecules in assays (column 1, lines 53-59).

Therefore, it would have been obvious to one of ordinary skill in the art to employ the method for producing protein-coated polystyrene microparticles of Vaynberg et al. to coat streptavidin that has been polymerized by chemical treatment, as taught by Desai et al. in order to produce microparticles that have a high capacity for capturing target molecules for use in assays. One would have reasonable expectation of success in employing the method of Vaynberg et al. with the polymerized streptavidin taught by Desai et al. because Desai et al. teach that polystyrene, which is the material taught in Vaynberg et al., is an appropriate solid phase for immobilization of polymerized streptavidin (see Desai at column 3, lines 42-44). In addition, while Vaynberg et al. only specifically teach the protein gelatin, Vaynberg et al. teach the adsorption of polyampholytes such as proteins in general (see p. 466, left column, first two paragraphs; and p. 471-472, "Conclusions").

27. Claims 10-12 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vaynberg et al. in light of Bocquier et al. and Bohidar or, alternatively, Lou et al. in light of Rossjohn et al. and Weis et al., and in view of Ryan et al. (US 6,462,809 B1).

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Vaynberg et al. and Lou et al. are as discussed above. The references fail to specifically teach that the coating steps are performed for 1-10 or 4-7 days; Vaynberg et al. teaches a time of 8-10 h (p. 467, the last three lines) and Lou et al. teach incubating for a “sufficient period of time”, which may be overnight or for 12-20 hours (column 5, lines 54-55; claim 9; and Example 1).

However, Ryan et al. teach that the adsorption of proteins onto polystyrene is affected by parameters such as pH, ionic strength, and period of incubation (column 14, lines 42-55).

Therefore, it would have been obvious to optimize the incubation time out of the normal desire of artisans to improve upon what is already known in light of the teachings of Ryan et al., which establish that incubation time is a result-effective variable for the adsorption of proteins onto polystyrene, which is the object of the methods of Vaynberg et al. and Lou et al.

With respect to claim 12, the Lou et al. reference teaches pH 8.5-11.9 and thereby meets the claim.

Although neither Vaynberg et al. nor Ryan et al. specifically teach a pH of 11-12, it would have been further obvious to employ, through routine optimization/ experimentation of the conditions of Vaynberg et al., pH 11-12 with a reasonable expectation of success, because of the normal desire of scientists or artisans to improve upon what is already generally known, as discussed above with respect to claim 1, and also in light of the teachings of Ryan that pH affects adsorption of proteins to polystyrene. In addition, one would be motivated to employ higher pH values because Vaynberg teaches that because hydrophobic effects dominate in adsorption of gelatin, increasing pH enables a denser layer of gelatin to form on the polystyrene (p. 471, left

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column, first full paragraph). One would have a reasonable expectation of success for the reasons discussed above with respect to claim 1.

28. Claims 10-12, 14, 16, and 18-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vaynberg et al. in light of Bocquier et al. and Bohidar or, alternatively, over Lou et al. in light of Rossjohn et al. and Weis et al., and in view of Schmid (DE 199 24 643 A1, Applicant's Information Disclosure statement of 5/6/04) and Ryan et al. Although a translation of the Schmid reference (which is in German) was not submitted, this rejection is being made pursuant to a consultation by the examiner with STIC translator J.M. Koytcheff.

Vaynberg et al. and Lou et al. are as discussed above. The references fail to specifically teach that the coating steps are performed for 1-10 or 4-7 days; Vaynberg et al. teaches a time of 8-10 h (p. 467, the last three lines) and Lou et al. teach incubating for a "sufficient period of time", which may be overnight or for 12-20 hours (column 5, lines 54-55; claim 9; and Example 1).

Vaynberg et al. and Lou et al. also fail to specifically teach that the pH of the protein-microparticle suspension or combination is adjusted to the recited pH values.

Schmid teach methods of coating microparticles with proteins by adsorption (column 1, lines 25-68). Specifically, Schmid teaches a method where microparticles are contacted with a protein in suspension, subjected to uniform heating for 10-90 minutes, maintained at the elevated temperature for 0-50 hours, and then irradiated with UV light (see the entire document, especially column 1, lines 1-11; column 3, lines 1-21; column 4, lines 5-43; the Example, and claim 1). The reference teaches that this process results in microparticles with high binding

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capacity and reduced bleeding, and allows for large-scale production. Suitable particles include DYNABEADS of size 2.7 microns and having 88% polystyrene and 12% magnetite (column 2, lines 29-35). The proteins to be coated are preferably hydrophobic, and have a size that can vary from 20-300 nm; a preferred size is 50-200 nm since a size ratio between particles and protein is preferably from >10:1 with >20:1 being particularly preferred (column 2, lines 36-68). The reference teaches that polymerized proteins strengthen the absorption and have a larger number of binding sites. Polymerized streptavidin (poly-SA) is specifically mentioned as having high binding capacity and low bleeding tendency (column 2, lines 59-68). The process allows for protein-charged microparticles useful as a test phase in medicinal, immunological, and diagnostic assays.

With respect to the incubation time, Schmid teaches that the microparticles and protein combined for 1-60 minutes before heating, uniformly heated for 10-90 minutes (preferably 10-60 minutes), then maintained at an elevated temperature of 25-70 degrees for a period of time sufficient for the desired adsorption; this period of time may be 0-50 hours or 1-20 hours (column 3, lines 1-21). The reference teaches that this time is important for the effectiveness of the method (column 4, lines 5-25).

Therefore, it would have been obvious to employ the heating and incubation steps taught by Schmid, in which the microparticle-protein combination is maintained at an elevated temperature for a period of time sufficient for desired adsorption, in the methods of Vaynberg et al. or Lou et al. because Schmid teaches that such steps result in microparticles with high binding capacity and reduced bleeding.

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With respect to claim 11, although Schmid et al. do not specifically teach a length of incubation that is 4-7 days, the reference establishes that incubation time is a result-effective variable. Further, Ryan et al. teach that incubation time is a parameter that affects adsorption of proteins to polystyrene (see especially column 14, lines 43-55). As such, it would have been obvious to optimize incubation time out of the normal desire of artisans to improve upon what is already known.

Regarding claims 14 and 18-19, it would have been further obvious to employ the microparticles taught by Schmid (2.8 microns in size, 88%/12% polystyrene/magnetite) and the polymerized streptavidin as the protein because Schmid teaches that these reagents produce protein-coated microparticles with strong adsorption, reduced bleeding, and high binding capacity that may be used for various applications including diagnostic assays.

With respect to the limitation that the pH is adjusted to the recited value as in claims 14 and 19, it is not considered an inventive difference to *adjust the pH of the microparticle-protein combination*, i.e. to adjust the pH **after** combining the microparticles with protein, as compared to adjusting the pH **before** combining these reagents. One skilled in the art would recognize that in order to carry out the coating reaction at the desired pH, the pH could be adjusted either before or just after mixing of the reaction components, so long as the mixture of reagents is at the desired pH while the coating reaction takes place. Moreover, the selection of any order of mixing ingredients is prima facie obvious. See MPEP 2144.04.

Thus, although Vaynberg et al. teach adding NaOH to gelatin and then combining gelatin with the microparticles in NaAc buffer (p. 468, left column, the first full paragraph), it would have been obvious to one of ordinary skill in the art to add NaOH either before or after mixing

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the components *in order to achieve the same purpose*, namely to maintain the reaction at the desired pH during the coating reaction.

Similarly, although Lou et al. teach that the coating reaction is maintained at the desired pH by diluting the protein into a buffered solution of the desired pH (column 4, lines 49-53; column 6, lines 29-31 and 40-42) before it is mixed with the microparticles, it would have been obvious to one of ordinary skill in the art that maintaining the pH of the microparticle-protein combination during the coating reaction could be performed in several ways in order to achieve this same desired result. One skilled in the art would immediately envisage that the pH could be adjusted either before (as in Lou et al.) or just after mixing of the reaction components, so long as the mixture of reagents is at the desired pH while the coating reaction takes place. As such, it would have been obvious to one of ordinary skill in the art to manipulate the reaction pH either before or after mixing the components *in order to achieve the same purpose*, namely to maintain the reaction at the desired pH during the coating reaction.

No criticality has been disclosed in the instant specification that would lead one skilled in the art to conclude that the pH must be adjusted to the desired level *after* combining the microparticles with the protein vs. adjusting the pH prior to combination as in Vaynberg et al. and Lou et al.

29. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Vaynberg et al. in light of Bocquier et al. and Bohidar, or, alternatively, over Lou et al. in light of Weis et al. and Rossjohn et al., and further in view of Bangs ("New developments in particle-based immunoassays: introduction" (1996) *Pure & Appl. Chem.* 10:1873-1879). Vaynberg et al. and

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Lou et al. are as discussed above, which fails to teach microparticles that have a magnetizable core.

However, Bangs teaches microparticles that have a magnetizable core (superparamagnetic particles and magnetic microspheres; see p. 1873, "Introduction," lines 1-4 and p. 1876, "Superparamagnetic Particle Based Assays") and their utility in fast and easy separation of solid and liquid phases, since they can be used to pull things out of solution quickly. The magnetic microparticles can be used in a variety of solid phase assays including ELISA and RIA.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to include the microparticles having a magnetizable core as taught by Bangs in the method for producing protein-coated polystyrene microparticles of Vaynberg et al. or, alternatively, Lou et al. because Bangs teaches the convenience of such microparticles in the fast and easy separation of solid and liquid phases. One would have a reasonable expectation of success because Bangs et al. teach that magnetic microparticles can be used in various types of solid phase assays.

30. Claims 15-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schmid in view of Vaynberg et al., Lou et al., and Serra et al. ("On the adsorption of IgG onto polystyrene particles: electrophoretic mobility and critical coagulation concentration" *Colloid Polym Sci* 270:574-583 (1992)).

Schmid teach methods of coating microparticles with proteins by adsorption (column 1, lines 25-68). Specifically, Schmid teaches a method where microparticles are contacted with a

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protein in suspension, subjected to uniform heating for 10-90 minutes, maintained at the elevated temperature for 0-50 hours, and then irradiated with UV light (see the entire document, especially column 1, lines 1-11; column 3, lines 1-21; column 4, lines 5-43; the Example, and claim 1). The reference teaches that this process results in microparticles with high binding capacity and reduced bleeding, and allows for large-scale production. Suitable particles include DYNABEADS of size 2.7 microns and having 88% polystyrene and 12% magnetite (column 2, lines 29-35). The proteins to be coated are preferably hydrophobic, and have a size that can vary from 20-300 nm; a preferred size is 50-200 nm since a size ratio between particles and protein is preferably from >10:1 with >20:1 being particularly preferred (column 2, lines 36-68). The reference teaches that polymerized proteins strengthen the absorption and have a larger number of binding sites. Polymerized streptavidin (poly-SA) is specifically mentioned as having high binding capacity and low bleeding tendency (column 2, lines 59-68). The process allows for protein-charged microparticles useful as a test phase in medicinal, immunological, and diagnostic assays.

The reference differs from the claimed invention in that it fails to specifically teach that the coating pH is 10-12.5. In Schmid, a pH of 7.0 is exemplified (the example).

However, it is known in the art that the pH at which proteins are coated onto polystyrene is a result-effective variable. For example, Vaynberg et al. (discussed above) teach that the properties of adsorbed proteins can vary in response to pH (p. 467, left column, the second paragraph). In the reference, increasing pH was found to be associated with a swelling of the hydrodynamic layer thickness, such that higher pH enabled a denser layer of protein to form on polystyrene (Figure 8, p. 470, right column, and p. 471, left column, the first full paragraph).

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Lou et al. (discussed above) also teach that adsorption pH can affect the stability of the adsorbed protein, reporting that by adsorbing streptolysin-O protein at alkaline pH of 8.5-11.9, the resulting product was more stable and the adsorbed protein substantially retained pre-adsorption characteristics (column 3, lines 34-38; column 4, lines 19-63; column 8, lines 53-59).

Similarly, Serra et al. teach that it is known that experimental conditions including ionic strength and pH can alter adsorption rate (see the paragraph bridging p. 576-577). For this reason Serra et al. performed experiments as in those in Vaynberg et al., varying the pH and incubation time of the coating reaction for coating IgG to polystyrene microparticles. Serra et al. report that in the case of IgG, increased ionic strength at pH values of 4 and 10 were associated with increased conformational stability of the protein (p. 579). The reference also teaches that the conformation of the adsorbed protein may depend on the adsorption pH and ionic strength (p. 582, left column).

Therefore, it would have been obvious to one of ordinary skill in the art to conduct the method of Schmid at the recited pH value as part of routine optimization, out of the normal desire of artisans to improve upon what is already known. It would have been obvious to do this since pH is known to have effects on the adsorption reaction of proteins to polystyrene as taught by Vaynberg et al., Lou et al., and Serra et al.

Moreover, Vaynberg et al. teaches that adsorption of protein onto polystyrene is dominated by hydrophobic interactions, such that there is little variation in the level of adsorption over a broad range of pH values, including alkaline pH values of up to pH 10 (see the entire document, especially at p. 467-468, "Adsorption Isotherms"; p. 469-470). Based on this teaching, one would have a reasonable expectation of success in optimizing the pH of the coating

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reaction in the method of Schmid as Vaynberg et al. teach that pH variations would not be expected to adversely affect the adsorption level.

With respect to claim 16, Schmid teaches that the microparticles and protein are subjected to uniform heating for 10-90 minutes and then maintained at the elevated temperature for 0-50 hours (column 2, lines 1-10, column 3, lines 1-21). The reference teaches that this time is important for the effectiveness of the method (column 4, lines 5-25). Although Schmid et al. do not specifically teach a length of incubation that is 4-7 days, the teaches establishes that incubation time is a result-effective variable. Serra et al. similarly teach that incubation time is a result-effective variable (see especially p. 577, right column). Therefore, in light of the fact that incubation time was known to have effects on protein adsorption to polystyrene, it would have been obvious to one of ordinary skill in the art to optimize the incubation time out of the normal desire of artisans to improve upon what is already known.

With respect to claim 17, Schmid teaches 50 mM K<sub>2</sub>HPO<sub>4</sub> (the example).

### *Response to Arguments*

31. Applicant's amendments and arguments in the amendment filed 10/04/06 have been fully considered.
32. With respect to the rejections of claims 1-3 and 5 under 35 USC 112 paragraph, written description (new matter), Applicant's arguments have been fully considered but they are not persuasive. Applicant argues that the Examiner has confused the notion of alternative embodiments and the concept of a "sub-genus", and that the facts of the case indicate that the pH

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range of 10.5 to 12.5 is simply an alternative pH range suitable for use with the invention (Applicant's arguments, p. 5-6).

With respect to the step of adjusting the pH to between 10.5 and 12.5 (see above and the previous Office action at p. 4-5), it is noted that the limitation was removed from claim 1 but is now recited in claim 14 (see Applicant's response, p. 5). Applicant argues that the subrange of pH 10.5-12.5 falls within the range of 10.0-12.5, which latter is disclosed in the summary of the invention. This argument is not on point because the limitation at issue is an **active method step** in which the pH is adjusted. The summary of the invention, in disclosing coating reactions "carried out at...pH...between 10.0 and pH 12.5" ([0015]) does not provide a written description for an active method step of adjusting the pH. There is no generic disclosure of adjusting the pH. The only description of adjusting the pH appears in specific examples, none of which involved adjusting the pH to the subrange currently claimed. Furthermore, the only disclosure of adjusting the pH involved specific reagents (i.e., adjusting the pH with NaOH), yet these accompanying limitations are not recited in the claims, such that the limitation of adjusting the pH represents a new subgenus not supported by the specification or claims as originally filed.

With respect to the subrange of pH 10.5-12.5 that is currently being claimed (see above and the previous Office action at p. 3-4), Applicant argues that this subrange is simply an alternative embodiment interchangeable with the larger range of pH 10-12.5 that is disclosed generically in the summary of the invention, to which the Examiner disagrees. Because the subrange of pH 10.5-12.5 is only disclosed in the specification in *limited contexts*, the introduction of this limitation into independent claim(s) represents a new subgenus not supported but the generic disclosure of pH 10.0-12.5 or by the specific examples in which pH 10.5-12.5 is

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mentioned in the specification. The fact that the subrange falls within the larger range does not automatically suggest, as Applicant appears to argue, that one skilled in the art would have understood the subrange to be interchangeable with the broader range in all contexts, given that this subrange is only mentioned in the context of long coating incubation times. The Examiner maintains that because the subrange is not disclosed generically, but is only mentioned in the specification in the context of long coating times, the facts of the case fail to support a determination that the subgenus currently being claimed is implicitly described by the specification.

Regarding Applicant's argument that paragraph [0030] of the specification associates the subrange of pH 10.5-12.5 with time intervals of 1-10 days as well as 4-7 days (see Applicant's reply at p. 6), the Examiner agrees that the paragraph could be reasonably interpreted in this manner. However, it is maintained for the reasons set forth in the rejection that the specification's specific description adjusting the pH of a combination of DYNAL M-270 or M-280 magnetic beads with polymerized streptavidin to between pH 10.0 and pH 12.5 does not provide support for the broader context in which pH is adjusted in claims 14 and 19.

33. With respect to the rejection of claim 2 under 35 USC 112 paragraph, written description (new matter), Applicant argues that compliance with 35 USC 112 does not require that applicants include in their specification that which is well known to the skilled practitioner, asserts that the use of chemical treatments to polymerized proteins is a well-established field, and cites MPEP 2163.05 (Applicant's arguments, p. 6-7). The arguments have been fully considered but they are not persuasive.

First, the matter at issue which is now being claimed is not simply “protein polymerized by chemical treatment” as argued by Applicant, but rather a method for coating microparticles as in claim 1 with “protein polymerized by chemical treatment”. Thus, the issue is not whether it was well known in the art to polymerize of proteins by chemical treatment, but rather, whether a method of coating microparticles by the method of claim 1 with such proteins was well known, which Applicant has elsewhere argued against.

Second, although that which is well known in the art need not be described *in detail* in the specification (MPEP 2163), in the instant case the genus that is currently being claimed (proteins polymerized by chemical treatment) has not been disclosed or described *at all* in the specification, which only discloses a species (streptavidin) reading on the genus of **proteins** now claimed. Notwithstanding that the genus is not disclosed in the specification or original claims, Applicant’s arguments that the disclosure of a single species supports the genus are unpersuasive. Although the Examiner agrees that there may be situations when a single disclosed species may support a genus claim, MPEP 2163.05 states that:

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species. A “representative number of species” means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

In the instant case, the Examiner disagrees that the disclosed species of **streptavidin** supports the genus of **proteins** polymerized by chemical treatment as claimed. One of ordinary skill in the art would recognize that such a genus is indeed characterized by substantial variation. Proteins have diverse functions in essentially all biological processes, functioning in catalysis, transport, mechanical support, immune protection, and other functions. Proteins also vary

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substantially with respect to structure; for example, some proteins are quite rigid while others have limited flexibility. For all these reasons, the Examiner maintains that one of ordinary skill in the art would not have understood the inventions to have possession of the genus encompassing *all proteins* polymerized by chemical treatment based on the written description of *streptavidin* polymerized by chemical treatment.

34. With regard to the rejection of claim 1 under 35 USC 103(a) above as being unpatentable over Vaynberg et al. and in light of the evidence of Bocquier and Bohidar, Applicant's arguments (p. 7-10) have been fully considered but they are not persuasive.

Applicant argues that the references do not teach or suggest a pH range of 10.5-12.5 (see p. 8), and further that that one skilled in the art would not reasonably consider the pH value of 10.5 to be "close enough" or "slightly higher" than pH 10 (as taught in the reference), to which the examiner disagrees for reasons of record. Furthermore, the arguments of counsel cannot take the place of factually supported objective evidence. See, e.g., *In re Huang*, 100 F.3d 135, 139-40, 40 USPQ2d 1685, 1689 (Fed. Cir. 1996); *In re De Blauwe*, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984). Applicant's assertion that one skilled in the art would not consider pH 10 to be "close" to pH 10.5 is unaccompanied by any evidence of record.

Furthermore, no criticality is disclosed in the instant specification for the currently claimed pH range as compared with the reference teaching. Rather, Applicant has elsewhere argued that pH 10-12.5 and pH 10.5-12.5 are interchangeable (see Applicant's reply, p. 6).

Applicant argues further that Vaynberg specifically teaches a maximum pH of 6.2 (see p. 8-9), which is not found persuasive for reasons of record (see the previous Office action at p. 16-18). Briefly, the examiner notes that this teaching must be read in the context of the reference as

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a whole. While Vaynberg et al. do report a maximum adsorption is around pH 6.2, this disclosure does not constitute a “teaching away” from higher pH values since the authors repeatedly emphasize that there was, in fact, “little variation” in terms of adsorption among the different pH values studied, and that “pH hardly affects the adsorption” (p. 470, left column). The authors conclude that hydrophobic effects dominate and that “pH variations do not affect gelatin adsorption” in the case of polystyrene (ibid). There is no teaching that adsorption is significantly affected at other pH values other than pH 6.2, and there is similarly no teaching that pH 6.2 represented a dramatic improvement over the other pH values tested, for example.

Therefore, Vaynberg et al. clearly provide the skilled artisan with a reasonable expectation of success in using the method over a wide range of pH values. It would have been obvious to one of ordinary skill in the art to employ a different pH, e.g. the slightly higher pH of 10.5, out of the normal desire of scientists or artisans to improve upon what is already generally known, and especially in light of the teaching by Vaynberg et al. that increasing pH enables a denser layer of gelatin to form on polystyrene, as noted above. As such, the reference also establishes that pH is a result-effective variable, since although pH hardly affected adsorption, it did achieve the recognized result of creating a denser layer of protein on the microparticles.

With respect to Applicant’s arguments that the examiner has not explained how a denser layer of protein achieved at higher pH as taught in Vaynberg would motivate someone attempting to adsorb more material with less bleeding onto a microparticle (see p. 9), it is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. There is no requirement that the prior art provide the same reason as the applicant to make the claimed invention. MPEP 2144.

Applicant further argues that the reference at most provides an invitation to experiment under an “obvious to try” standard (see p. 9), to which the examiner disagrees since in this case there is both motivation (normal desire to improve on what is already known, as well as to obtain a denser layer of protein) and as an expectation of success (“little variation” in terms of adsorption levels vs. pH). Thus, the rejection of record cannot be properly categorized in this fashion.

35. With respect to the rejection of claim 2 under 35 USC 103(a) as being unpatentable over Vaynberg in view of Tischer et al., and of claim 3 as being unpatentable over Vaynberg in view of Desai, Applicant does not separately argue the limitation of these dependent claims (see p. 10-11).

36. With respect to the patentability of new claims 15-19, Applicant argues (see p. 10) that Vaynberg does not teach or suggest a pH range of 10.5-12.5, which is not relevant because these claims recite a pH range of 10-12.5 rather than 10.5-12.5.

37. With respect to the rejections of claims 1-2 under 35 USC 103(a) as being unpatentable over Lou et al. and in light of the evidence of Weis and Rossjohn, Applicant argues (see p. 11-13) that the protein of Lou et al. (streptolysin-O) does not meet the claim limitation of having “a size from 10 nm to 300 nm *as determined by photon correlation spectroscopy*”.

First, Applicant’s arguments that one skilled in the art would not conclude that perfringolysin-O and streptolysin-O have the same size without actual data (see p. 12) are unsupported by evidence. The evidence of record (Weis et al.) establishes the two proteins are highly homologous and expected to have “very similar 3D structures”. Thus, the factual evidence of record establishes that it is proper to make inferences about the structure of streptolysin-O

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based on the structure of the homologous protein perfringolysin-O. Since Rossjohn et al. teaches that the size of perfringolysin-O is within the recited range, it would be expected that streptolysin-O would also have a size within the recited range. As a result, the examiner maintains that the evidence of record reasonably supports the determination that streptolysin-O meets the claim limitation of being a protein within the recited range.

Second, the position being taken by Applicant that different methods known in the art for measuring protein size would not be expected produce the same results (see p. 12) is unsupported by any evidence of record. The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965).

One skilled in the art would recognize that a protein's size is an inherent characteristic, one that may be measured by a number of different techniques. Although it is conceivable that different techniques might produce different measurements (for example, within experimental error), there is no factual evidence of record to support this position, and in particular, no evidence of record to suggest that photon correlation spectroscopy would produce measurements that differ significantly from other techniques. To the contrary, the prior art recognizes that both photon correlation spectroscopy and X-ray crystallography (as in Rossjohn) produce accurate measurements of a protein's size that agree well with each other. For example, Kadima et al. (*Biophys. J.* Vol. 57 (1990), p. 125-132) examined the size of the protein canavalin by both of these techniques, and found that the two measurements were **"equal within the limits of experimental error"** (see especially at p. 128).

In addition, Applicant's argument that protein size should be determined by photon correlation spectroscopy is not persuasive because the claims do not recite a step of determining

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size by photon correlation spectroscopy. The reference to this technique is only in reference to the size of the protein to be coated (an inherent characteristic of the protein), and therefore is not entitled to weight in the claim. For all of these reasons, in order to meet the claim limitation, a protein need not have its size measured by the specific technique of photon correlation spectroscopy since the claims do not recite any step in which this technique is actually employed.

38. Applicant argues that new claims 15-19 are patentable over Lou et al. because neither Lou et al. nor the evidentiary references (Weis et al. and Rossjohn et al.) teach a method where the pH of the suspension is between 10.5 and 12.5 (see Applicant's reply at p. 13), which is not relevant because the claims recite a pH range of 10.0-12.5.

39. With respect to the rejection of claim 5, Applicant does not separately argue the limitations of the dependent claim (see p. 13-14).

### ***Conclusion***

40. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Vaynberg et al. (*Journal of Colloid and Interface Science* 205 (1998), 131-140) is also cited with respect to new claim 9 for its teaching of size measurement of gelatin (the protein employed by Vaynberg et al. above); Vaynberg et al. '98 report a hydrodynamic radius of 20 nm, which is in agreement with the Bohidar reference discussed above (see the paragraph bridging the left and right columns of p. 135).

41. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 8:30-5. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached at (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Christine Foster, Ph.D.  
Patent Examiner  
Art Unit 1641



LONG V. LE 11/24/06  
SUPERVISORY PATENT EXAMINER  
TECHNOLOGY CENTER 1600